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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/644,587	SANCHEZ ET AL.	
	Examiner	Art Unit	
	Roy P. Issac	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 August 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *20,22-25,27-30 and 32-34* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *20, 22-25, 27-30, 32-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Office Action is in response to Applicant's amendment/ remarks/ response filed 8/08/2007, wherein claim 22 have been amended. Claims 20, 22-25, 27-30 and 32-34 are currently pending and are examined on the merits herein.

Applicant's declarations filed as appendixes A and B, are acknowledged and will be further discussed below.

Rejections Withdrawn

The terminal disclaimer filed on 8/8/2007 disclaiming the terminal portion of any patent granted on this application, which would extend beyond the expiration date of application No 10/644,579 has been reviewed and is accepted. The terminal disclaimer has been recorded.

The terminal disclaimer filed on 8/8/2007 with respect to the rejection of claims 20, 22-25, 27-30 and 32-34 made under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 20-40 of the copending application No. 10/544, 579 of record in the previous Office Action dated 2/2/2007, has been considered and found persuasive. Therefore, this obviousness-type double patenting rejection is withdrawn.

Applicants' amendment to claim 22 deleting the phrase, "or less" and inserting the range "2.5 to 7.5 mg" overcomes the rejection under section 112, second paragraph.

The following are new or modified rejections necessitated by Applicant's amendment filed 8/8/2007, wherein the limitations in pending claims 22 as amended now have been changed and claims 23-24, 27-30 and 32-34 depend from claim 22. The limitations in the amended claims have been changed and the breadth and scope of those claims have been changed. Therefore, rejections from the previous Office Action, mailed 02/02/2007, have been modified and are listed below.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 20, 22-25, 27-30 and 32-34 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant's amendment with respect to amended claims herein has been fully considered but is deemed to insert new matter into the claims since the specification as originally filed does not provide support for a "daily dose of 2.5 to 10 mg" or a "daily dose of 2.5 to 7.5 mg". The original specification clearly

discloses "dose of 10 mg" (Page 3, lines 22-26), "daily doses lower than 10 mg" (Page 5, lines 32-34), and a unit dose preparation of 2.5 to 20 mg. (Page 5, lines 29-30). The range instantly claimed "daily dose of 2.5 to 10 mg" is not disclosed in the specification as originally filed. The species "daily dose of 2.5 mg" is not disclosed in the specification. The disclosed "unit dose preparation of 2.5 to 20 mg" cannot be considered as a "daily dose" since a patient can take more than one "unit dose preparations" per day. One skilled in the art will clearly recognize that a "unit dose preparation" is not the same as a "daily dose". Adequate written description means that, in the specification, the applicant must "convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the [claimed] invention." Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555, 1563-64 [19 USPQ2d 1111] (Fed. Cir. 1991). When no such description can be found in the specification, the only thing the PTO can reasonably be expected to do is to point out its nonexistence. In re Alton, 76 F.3d 1168, 1175 [37 USPQ2d 1578] (Fed. Cir. 1996).

Furthermore, if the range claimed herein is considered not to have adequate written description support, even if it is considered as a subgenus of one of the disclosed ranges. The court held that "subgenus range was not supported by generic disclosure and specific example within the subgenus range"; See, e.g., *In re Lukach*, 442 F.2d 967, 169 USPQ 795 (CCPA 1971); the court also held that "a subgenus is not necessarily described by a genus encompassing it and a species upon which it reads" (see *In re Smith*, 458 F.2d 1389,1395, 173 USPQ 679, 683 (CCPA 1972). See also MPEP 2163.

Consequently, there is nothing within the instant specification which would lead the artisan in the field to believe that Applicant was in possession of the invention as it is now claimed. See *Vas-Cath Inc. v. Mahurkar*, 19 USPQ 2d 1111, CAFC 1991, see also *In re Winkhaus*, 188 USPQ 129, CCPA 1975.

What the applicant have done is to pick characteristics possessed by two disclosed numerical ranges, one disclosed as a daily dose and the other as a unit dose preparation, and then make it the basis of claims that cover a new range. This is exactly the type of overreaching the written description requirement was designed to guard against. See Vas-Cath, 935 F.2d at 1561, 19 USPQ2d at 1115 ("Adequate description of the invention guards against the inventor's overreaching by insisting that he recount his invention in such detail that his future claims can be determined to be encompassed within his original creation.") (*quoting* Rengo Co. v. Molins Mach. Co., 657 F.2d 535, 551, 211 USPQ 303, 321 (3d Cir. 1981)).

Response to Arguments

Applicant's arguments filed 8/8/07 have been fully considered but they are not persuasive. Applicants argue that, the cited cases *In re Lukach* and *In re Smith* does not support for the assertion that a subgenus is not supported by the disclosure of a generic range even if specific values within the generic range are also disclosed. Applicants' submission of the two cases as Appendix A and B, is fully considered and found unpersuasive. The following is a passage from MPEP 2163(B):

> Thus, the written description requirement prevents an applicant from claiming subject matter that was not adequately described in the specification as filed. New or amended claims which introduce elements or limitations which are not supported by the as-filed disclosure violate the written description requirement. See, e.g., *In re Lukach*, 442 F.2d 967, 169 USPQ 795 (CCPA 1971) (subgenus range was not supported by generic disclosure and specific example within the subgenus range); *In re Smith*, 458 F.2d 1389, 1395, 173 USPQ 679, 683 (CCPA 1972) (a subgenus is not necessarily described by a genus encompassing it and a species upon which it reads).

The holdings of the two cited cases supports the asserting that a subgenus is not necessarily described by a genus encompassing it and a species upon which it reads.

Applicants further argue that persons skilled in the art would consider a daily dose of 2.5 to 10 mg per day of escitalopram as part of tehinvention because the specification discloses a daily dose of lower than 10 mg per day, specific daily doses of 7.5 and 5 mg per day and a unit dose preparation of 2.5 to 20mg. The 2.5 to 20 mg range is directed toward a unit dose preparation and is separate from the daily doses. The only daily doses disclosed are 7.5 and 5 mg and the range of lower than 10 mg per day. The lower limit for daily dose claimed herein, 2.5 mg, is not recited in the specification. Thus the range claimed for daily dose is clearly not supported by the specification.

Applicant is reminded that written description requirement of 35 U.S.C. §112 exists independently of enablement requirement, and invention that is enabled may nonetheless be held invalid for failure to meet written description requirement. Provisions of 35 U.S.C. §112 impose written description

requirement separate and apart from enablement requirement, and conclusive evidence of claim's enablement is not equally conclusive of that claim's satisfactory written description.

The original patent specification must therefore "'describe the claimed invention so that one skilled in the art can recognize what is claimed.'" Koito Mfg. Co., Ltd. v. Turn Key Tech, LLC, 381 F.3d 1142, 1154 [72 USPQ2d 1190] (Fed. Cir. 2004) (quoting Enzo Biochem, Inc. v. Gen-Probe Inc., 323 F.3d 956, 968 [63 USPQ2d 1618] and [63 USPQ2d 1609] (Fed Cir. 2002)). "In evaluating whether a patentee has fulfilled this requirement, our standard is that the patent's 'disclosure must allow one skilled in the art' to visualize or recognize the identity of the subject matter purportedly described." Koito, 381 F.3d at 1154 (citations omitted). In the absence of a disclosure of the range claimed herein, "daily dose of 2.5 to 10 mg" one of skill in the art would not recognize the applicants' to have had possession of the invention as claimed.

Adequate written description means that, in the specification, the applicant must "convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the [claimed] invention." Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555, 1563-64 [19 USPQ2d 1111] (Fed. Cir. 1991). When no such description can be found in the specification, the only thing the PTO can reasonably be expected to do is to point out its nonexistence. In re Alton, 76 F.3d 1168, 1175 [37 USPQ2d 1578] (Fed. Cir. 1996).

The rejection under section 112, first paragraph for the lack of written description support is deemed proper and is adhered to.

Claims 20, 22-25, 27-30 and 32-34 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had full possession of the claimed invention.

The instant application claims a method of treating a patient suffering from depression who has a sleep disturbance when treated with a selective serotonin reuptake inhibitor other than escitalopram without inducing sleep disturbance comprising administering a daily pharmaceutically effective amount of escitalopram. The only mention of "sleep disturbances" in the application follows; "As a further advantage, the fact that escitalopram is effective in lower doses suggests that effective treatment with less side effects may be obtained, in particular, a reduced amount of serotonin reuptake inhibitor **may reduce the risk of SSRI-induced sexual dysfunction and sleep disturbances**." (emphasis added). The disclosure is merely speculating that a lower dosage use *may* have beneficial effects. There is no showing of the use of escitalopram in any patients who have suffered from sleep disturbance. The claim herein is directed to "a patient suffering from depression who has **a sleep disturbance**". Here there is no showing that the patients have not suffered even one instance of "a sleep disturbance" as claimed herein. Thus, one of ordinary skill in the art would not believe that the applicant had full possession of the invention as claimed.

Response to Arguments

Applicant's arguments filed 8/8/2007 have been fully considered but they are not persuasive. Applicants argue that, the applicant need not provide evidence of either conception or actual reduction to practice when relying on the content of the patent application. However, the content of the patent application is clearly lacking in support of applicants' claims herein. Applicants' further argue that the disclosure stating, "the fact that escitalopram is effective in lower doses suggests that effective treatment with less side effects may be obtained, in particular, a reduced amount of serotonin reuptake inhibitor may reduce the risk of SSRI induced sexual dysfunction and sleep disturbances", provides adequate written description support for the claims herein. The statement is clearly speculative, and one of skill in the art would not consider the above statement to have put the applicants' in possession of the invention claimed herein. Furthermore, the disclosure is directed to "sleep disturbances" while the claims herein are directed to "a sleep disturbance".

The original patent specification must therefore "'describe the claimed invention so that one skilled in the art can recognize what is claimed.'" Koito Mfg. Co., Ltd. v. Turn Key Tech, LLC, 381 F.3d 1142, 1154 [72 USPQ2d 1190] (Fed. Cir. 2004) (quoting Enzo Biochem, Inc. v. Gen-Probe Inc., 323 F.3d 956, 968 [63 USPQ2d 1618] and [63 USPQ2d 1609] (Fed Cir. 2002)). "In evaluating whether a patentee has fulfilled this requirement, our standard is that the patent's 'disclosure must allow one skilled in the art' to visualize or recognize the identity of the subject matter purportedly described." Koito, 381 F.3d at 1154 (citations

omitted). In evaluating the original disclosure as a whole, one of skill in the art would not recognize that the applicants were in possession of the invention as claimed herein, i.e., "treating a patient suffering from depression who has a sleep disturbance".

Adequate written description means that, in the specification, the applicant must "convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the [claimed] invention." Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555, 1563-64 [19 USPQ2d 1111] (Fed. Cir. 1991). The speculation that lower dosage may reduce sleep disturbances does not convey to one of skilled in the art with clarity that, as of the filing date sough, the applicant was in possession of the claimed invention. When no such description can be found in the specification, the only thing the PTO can reasonably be expected to do is to point out its nonexistence. *In re Alton*, 76 F.3d 1168, 1175 [37 USPQ2d 1578] (Fed. Cir. 1996). The rejection under section 112, first paragraph is still deemed proper and is adhered to.

Claims 20, 22-25, 27-30 and 32-34 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the treatment of depression with escitalopram, does not reasonably provide enablement for a method of treating a patient suffering from depression who has a sleep disturbance when treated with a selective serotonin reuptake inhibitor other than

escitalopram without inducing sleep disturbance comprising administering a daily pharmaceutically effective amount of escitalopram. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The instant specification fails to provide information that would allow the skilled artisan to practice the instant invention. Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

(1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

Nature of the invention:

The instant application relates to a method for treating a patient suffering from depression who has a sleep disturbance when treated with a selective serotonin reuptake inhibitor other than escitalopram without inducing a sleep disturbance comprising administering escitalopram.

The relative skill of those in the art:

The relative skill of those in the art is high, with a typical practitioner having obtained a PhD, M.S. or equivalent advanced degree.

Breadth of the claims

The claims are deemed very broad since, the claim encompasses any patient who has suffered from *even one instance of depression* when treated with a SSRI other than escitalopram. The claims encompasses both known SSRIs as well as those not yet discovered. In order to determine which of the thousands of SSRIs has produced at least one sleep disturbance one of skill in the art would have to conduct extensive studies of those SSRIs.

The presence or absence of working examples and the amount of direction or guidance presented:

The applicants disclose a clinical study for the treatment of **depression** using escitalopram and citalopram. (Page 6, lines 20-page 7). The study compared escitalopram and citalopram for **depression** using the MADRS scale. However, the study does not disclose the treatment of any patients suffering from depression who has a sleep disturbance when treated with an SSRI other than escitalopram without inducing a sleep disturbance. In view of any disclosure showing a treatment of any patients suffering from depression who has a sleep disturbance when treated with an SSRI other than escitalopram without inducing a sleep disturbance, one of skill in the art will have to conduct extensive research efforts.

The predictability or lack thereof in the art and the quantity of experimentation necessary:

The disclosure do not contain any examples of the treatment of "a patient suffering from depression who has a sleep disturbance." There is no indication that any of the patients have had even used other SSRIs prior to entering into the clinical trials herein. As such, there is no indication that they suffered from sleep disturbances. The lack of working examples is a critical and crucial factor to be considered, especially in cases involving an unpredicatable and undeveloped art. See MPEP § 2164.

It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. *In re Fisher*, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. In the instant case, the instant claimed invention is highly unpredictable since one skilled in the art would recognize that the recitation, "selective serotonin reuptake inhibitor" encompasses thousands of compositions with varying effects and unknown side effects. As such, each composition will need to be individually evaluated for activity in regards to sleep disturbance. There are thousands of SSRIs known in the literature and more are currently being developed. In order to practice the invention as claimed herein, one of skill in the art will need to first determine if after treatment with a particular SSRI, whether a patient has had at least one sleep disturbance.

In order to determine how the patients can be treated without inducing even one instance of sleep disturbance, one of skill in the art will have to conduct

extensive research including extensive intellectual input from highly trained scientists and medical doctors.

Thus, the specification fails to provide clear and convincing evidence in sufficient support for the treatment of a method for treating a patient suffering from depression who has a sleep disturbance when treated with a selective serotonin reuptake inhibitor other than escitalopram without inducing a sleep disturbance.

Genentech, 108 F.3d at 1366, sates that, "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion." And "patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable."

Therefore, in view of the *Wands* factors as discussed above, to practice the claimed invention herein, a person of skill in the art would have to engage in ***undue experimentation*** to practice the invention commensurate in scope with the claims.

Response to Arguments

Applicant's arguments filed 8/8/07 have been fully considered but they are not persuasive. Applicants argue that, working examples are not required in order to satisfy the enablement requirement. However, the lack of working examples is one of the factors considered in combination with other factors discussed in the above rejection. The lack of working examples is a critical and

crucial factor to be considered, especially in cases involving an unpredicatable and undeveloped art. See MPEP § 2164. Applicants further argue that the examiners assertion that thousands of compounds will need to be evaluated is unwarranted in view of the small range of escitalopram claimed herein. However, there are thousands of SSRIs known in the literature and more are currently being developed. In order to practice the invention as claimed herein, one of skill in the art will need to first determine if after treatment with a particular SSRI, whether a patient has had at least one sleep disturbance. Such experimentation cannot be considered routine and involves extensive clinical research. The rejection under section 112, first paragraph is still deemed proper and is adhered to.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 20, 22-25, 27-30 and 32-34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Boegesoe et.al. (U.S. Patent # RE 34,712) or Boegesoe et.al, (EP Publication # 0347066 B1, 1995) in view of Bouchard et.al. (PTO-

1449, Of Record), further in view of Merck Manual. (Page 440, Column 2, paragraph 2; PTO-892, Cited by the examiner).

The '712 patent describes the synthesis and use of escitalopram for depression. (Column 1, lines 13-35). The '712 patent discloses a method for using escitalopram and its non-toxic addition salts, such as oxalate salt, and crystallization. (See Column 1, line 45-46). The '712 patent further teaches the use of a pharmaceutically effective amount of escitalopram and discloses 5-50mg daily dosage, in particular 5mg. (See example at Column 9, line 10). Furtheremore, the '712 patent discloses a method for using escitalopram and its non-toxic addition salts, such as oxalate salt, and crystallization. (See Column 1, line 45-46). The '712 patent further teaches the use of a pharmaceutically effective amount of escitalopram and discloses 5-50mg daily dosage, in particular 5mg. (See example at Column 9, line 10)

Boegesoe et. al. does not expressly disclose the treatment of a patient suffering from depression who has a sleep disturbance when treated with a selective serotonin reuptake inhibitor other than escitalopram or the daily dose of 7.5mg.

Bouchard et.al. teach the use of citalopram because of its low side effects in patients with depression. The authors note that; "Single MADRS-items analyses revealed a better effect of citalopram on "reduced appetite" on day 14 and 42, "apparent sadness", "reduced sleep" and "suicidal thought" on day 42." (Pg. 57, Col1, lines 32-40).

Merck manual of diagnostics note that, "Most depressed people have difficulty falling asleep and awaken repeatedly particularly early in the morning." (Page 440, Column 2, paragraph 2; PTO-892, Cited by the examiner).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use a daily dose of 5-10mg, such as 7.5mg, of escitalopram or its oxalate salt for the treatment of patients suffering from depression who have sleep disturbances when treated with a selective serotonin reuptake inhibitor other than escitalopram without inducing sleep disturbances.

One of ordinary skill in the art would have been motivated to treat patients with escitalopram in daily dosage ranges of 2.5-10mg, including 7.5mg, for patients suffering from depression who have sleep disturbances when treated with a selective serotonin reuptake inhibitor other than escitalopram without inducing sleep disturbances, because citalopram has advantages as an antidepressant with low sleep disturbance and because citalopram's pharmacological activity is attributed to its escitalopram enantiomer. The instant claimed range of 10mg or less overlaps with the 2.5-50mg disclosed in Boegesoe. If the claimed ranges "overlap or lie inside ranges disclosed by the prior art" a *prima facie* case of obviousness exits. See *In re Woodruff,* 919 F.2d 1575, 16 USPQ2d 1934 (Fed. Cir 1990). See MPEP § 2144.05 [4-1]. Furthermore, a person of ordinary skill in the art has good reason to pursue the known options within his or her technical grasp, such as lowering the dosage to achieve reduced side effects. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. Using the

recognized active enantiomer of a compound in view of success with the racemic mixture of the compound itself is nothing more than one of ordinary skill in the art using a particular known technique recognized as part of the ordinary capabilities of one skilled in the art.

Therefore one of ordinary skill in the art would have reasonably expected that the use of escitalopram for the treatment of patient suffering from depression who has a sleep disturbance when treated with a selective serotonin reuptake inhibitor would result in reduced sleep disturbance.

Thus, the claimed invention as a whole is clearly *prima facie* obvious over the combined teachings of the prior art.

Response to Arguments

Applicant's arguments filed 8/8/07 have been fully considered but they are not persuasive. Applicants argue that, Bouchard teaches the administration of citalopram (not escitalopram). However, escitalopram is the active enantiomer the racemic citalopram. The claims herein use the open transitional phrase "comprising" which does not preclude the presence of the inactive enantiomer, and thus citalopram itself is considered to comprise escitalopram.

Applicants argue that Bouchard teaches that administration of citalopram leads to improvement in reduced sleep but only at a higher dosage level. However, Boegesoe discloses ranges overalapping or encompassing the range claimed herein. Applicants argument that based on Bouchard's fixed dose study, one or ordinary skilled in the art would have been disinclined to use a lower

dosage. This argument was found unpersuasive since Boegesoe teaches lower dosages and one of ordinary skill in the art would have expected lower doses to reduce side effects such as sleep disturbances even further. A person of ordinary skill in the art has good reason to pursue the known options within his or her technical grasp, such as lowering the dosage to achieve reduced side effects. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. Applicants' further argue that that fact that the references can be combined does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. *KSR v. Teleflex* forecloses the argument that a specific teaching suggestion or motivation is required to support a finding of obviousness. (See *KSR v. Teleflex*, 82 USPQ2d at 1396). The rejection under section 103(a) is still deemed proper and is adhered to.

Claims 20, 22-25, 27-30 and 32-34 are further rejected under 35 U.S.C. 103(a) as being unpatentable over Feighner, JP et. al. (PTO-892, Of record), in view of Hyttel, J. et. al. (PTO-1449, Of record) further in view of Schoffers et. al. (PTO-892, Of record).

Feighner et. al disclose the use of racemic citalopram for moderate-to-severe depression in dosage levels ranging from 10mg to 60mg. One skilled in the art would recognize that a racemic mixture contains two enantiomers of a

compound in its (+) and (-) form. The (+) and (-) designate the optical activity of the compound. Generally, a racemic mixture has both enantiomers in about equal proportions. Thus, a 10mg dose of racemic citalopram should contain 5mg of its (+) enantiomer and 5mg of its (-) enantiomer. The chiral dosage range of (+)-citalopram in Feigner's study is estimated to be 5-30mg. The authors also disclose the use of citalopram in patients who have been treated with other antidepressants. (Page 826, Table 1, line 6). The study also shows a decrease in insomnia in patients treated with citalopram at lower dose levels. (Page 828, Table 3, line 3). The length of the study was six-weeks. (Page 824, Column 1, Paragraph 3).

Feighner et. al. does not disclose the use of the escitalopram ((+)-citalopram), as the applicant define that esctialopram refers to one of the enantiomers of *S*- or (+)-citalopram. (Specification, Page 1, line 3-5). Feigner et. al. does not disclose the use of oxalate salt or the oxalate salt in its crystalline form.

Hyttel et. al teach the use of (+)-citalopram, and its crystallized oxalate salt, and shows that the pharmacological activity of the racemic citalopram is attributed to one of its enantiomers, (+)-citalopram, also known as escitalopram. (See Pg.157, lines 10-14, and Pg. 158, lines 25-29).

Schoffers et. al teach the advantages of using chirally pure compounds as pharmaceuticals. The author notes: "An increasing interest in understanding biological processes and the general recognition that chirality plays a crucial role in nature fostered tremendous effort in enantioselective synthesis. In the course

of synthesizing natural products and designing new target compounds, chemists had to acknowledge the fact that enantiopurity is related to biological processes. Opposite enantiomers interact differently within an organism and can display various activities." (See Page 3770, lines 3-12). Furthermore, the advantages of using chirally pure drugs are well known in the art.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use a daily dose of 5-10mg of (+)-citalopram or its oxalate salt for the treatment of patients suffering from depression who have sleep disturbances when treated with a selective serotonin reuptake inhibitor other than escitalopram without inducing sleep disturbances.

One having ordinary skill in the art would have been motivated to treat patients with depression who have sleep disturbances when treated with a selective serotonin reuptake inhibitor other than escitalopram without inducing sleep disturbances comprising administering a daily pharmaceutically effective amount of escitalopram, because decreasing dose levels in citalopram leads to reduced side effects, and it is effective in daily dose ranges of 10-60mg or 5-30mg of (+)-citalopram. One skilled in the art would be further motivated to use (+)-citalopram or its oxalate salt because of the advantages of using a chirally pure drug and due to Hyttel's showing that the pharmacological activity resides in (+)-citalopram enantiomer. The instant claimed range of 10mg or less overalps with the 10-60mg (5-30mg chiral dosage) disclosed in Feigner. If the claimed ranges "overlap or lie inside ranges disclosed by the prior art" a *prima facie* case of obviousness exits. See *In re Woodruff,* 919 F.2d 1575, 16 USPQ2d 1934

(Fed. Cir 1990). See MPEP § 2144.05 [4-1]. Furthermore, a person of ordinary skill in the art has good reason to pursue the known options within his or her technical grasp, such as lowering the dosage to achieve reduced side effects. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. Using the recognized active enantiomer of a compound in view of success with the racemic mixture of the compound itself is nothing more than one of ordinary skill in the art using a particular known technique recognized as part of the ordinary capabilities of one skilled in the art.

Therefore one of ordinary skill in the art would have reasonably expected that the use of escitalopram for the treatment of patient suffering from depression who has a sleep disturbance when treated with a selective serotonin reuptake inhibitor would result in reduced sleep disturbance.

Thus, the claimed invention as a whole is clearly *prima facie* obvious over the combined teachings of the prior art.

Response to Arguments

Applicant's arguments filed 8/8/07 with respect to this rejection under 35 U.S.C 103(a) of record in the previous Office Action have been fully considered but they are not deemed persuasive to render the claimed invention patentable over the prior art as further discussed below.

Applicants argue that Feigner et. al. teaches away from using Citalopram, the racemic mixture of the active enantiomer escitalopram, by disclosing insomnia as a side effect among other side effects. This argument was found

unpersuasive since Feigner shows that reduced dosage decreases insomnia. One of ordinary skill in the art would have expected the single enantiomer, escitalopram to be effective with even lower dosage and thus further reducing insomnia. Feigner et. al. teaches citalopram to be significantly more effective than placebo in teaching depression and Merck Manual discloses sleep disturbances as associated with depression. The insomnia incidents disclosed in patients (11 in placebo and 13 in citalopram at 10 mg dosage level), would have been expected to reduce further by the lower dosage afforded by escitalopram. The rejection under section 103(a) is still deemed proper and is adhered to.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory

action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Roy P. Issac whose telephone number is 571-272-2674. The examiner can normally be reached on 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Anna Jiang can be reached on 571-272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

10/11/07

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